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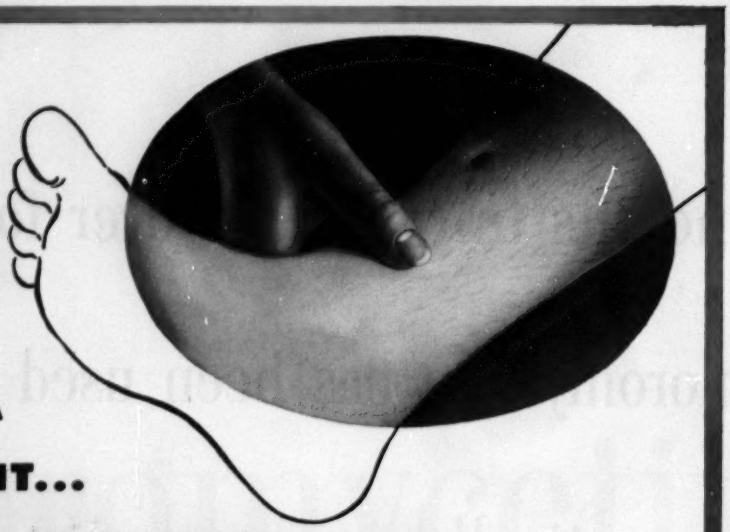

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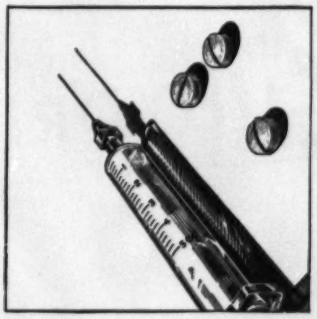

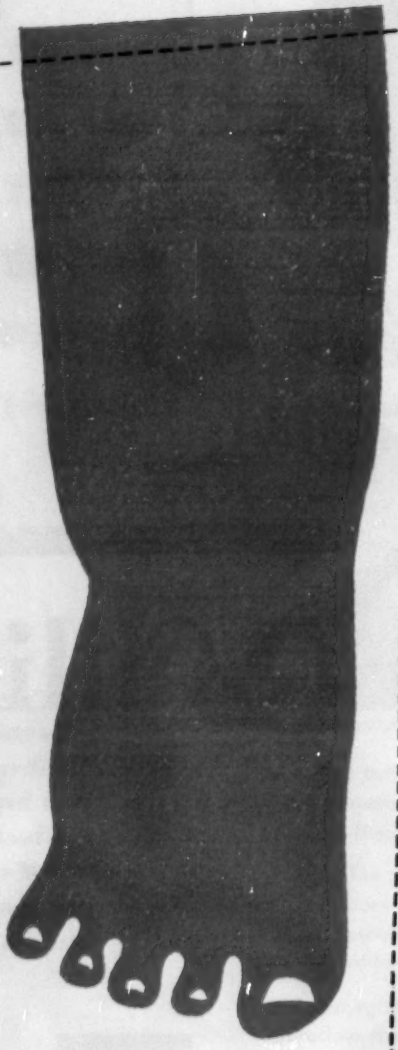

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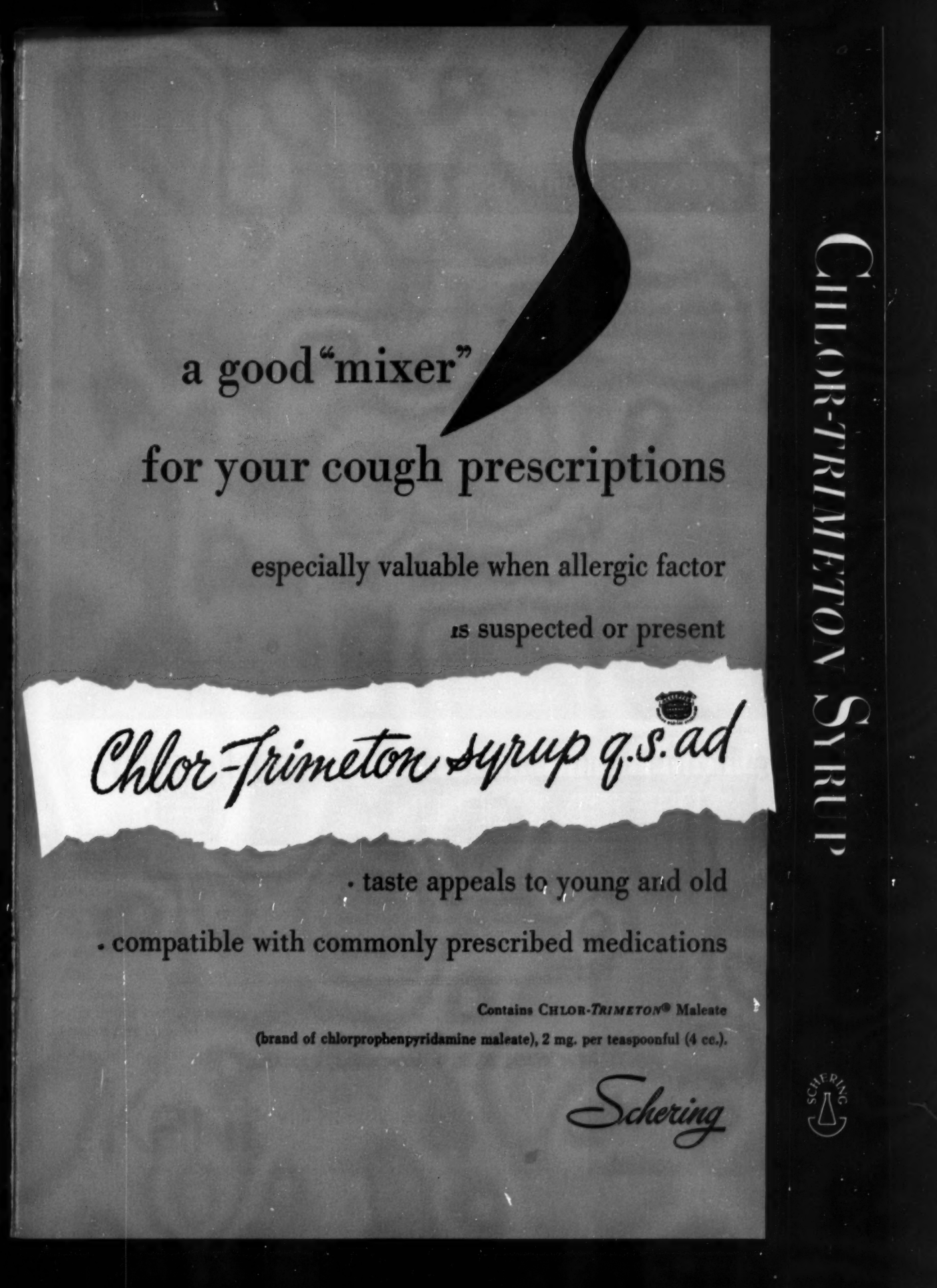
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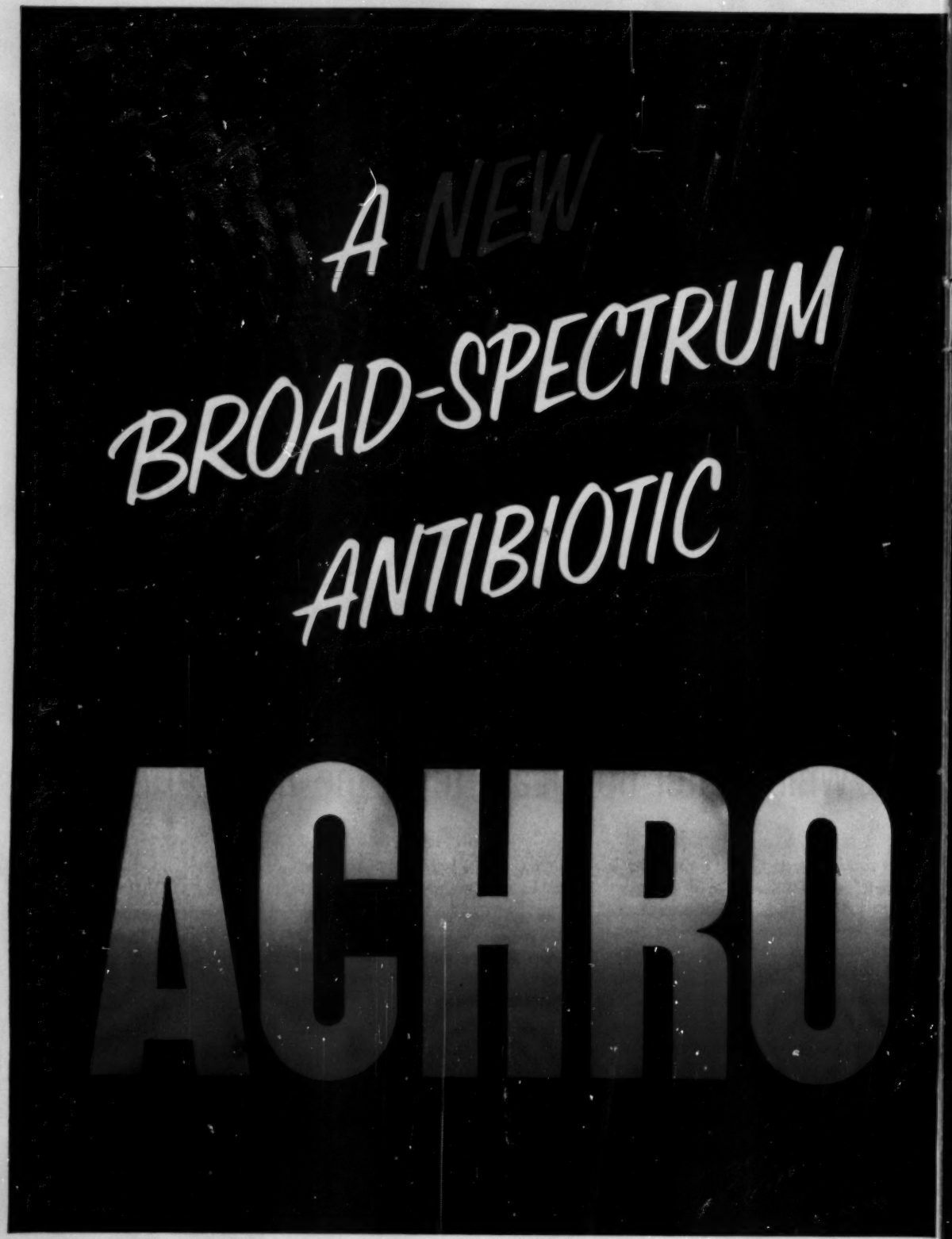
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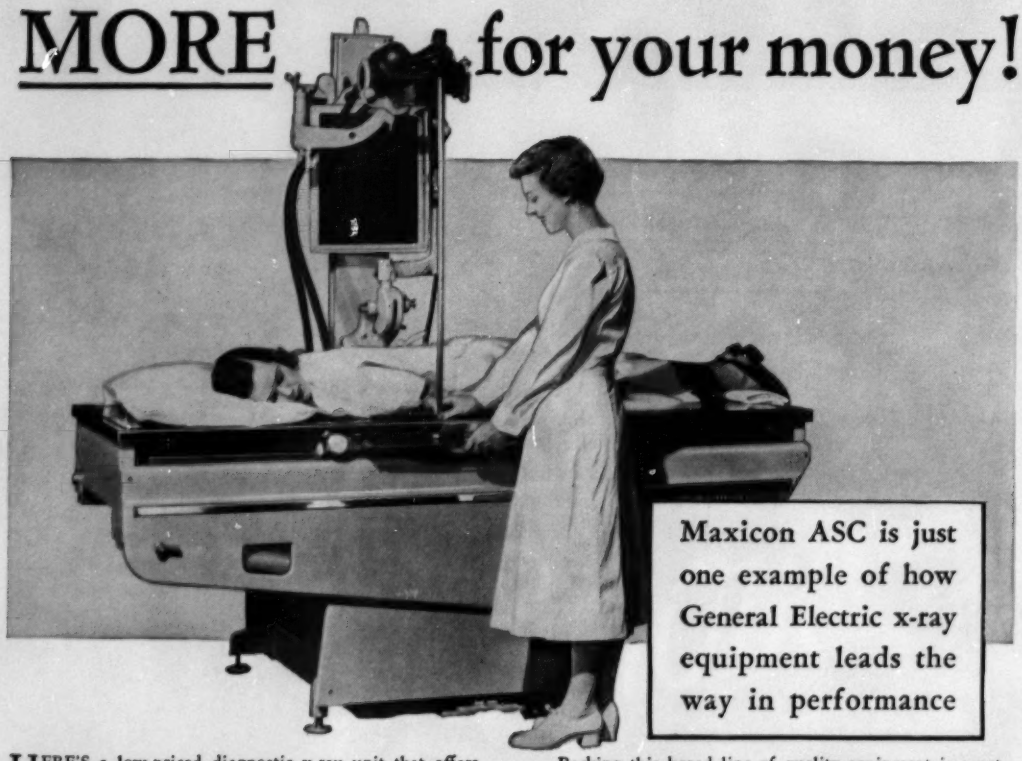

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1. Sayer, R. J., et al.: Am. J. M. Sc. *221*:256 (Mar.) 1951.
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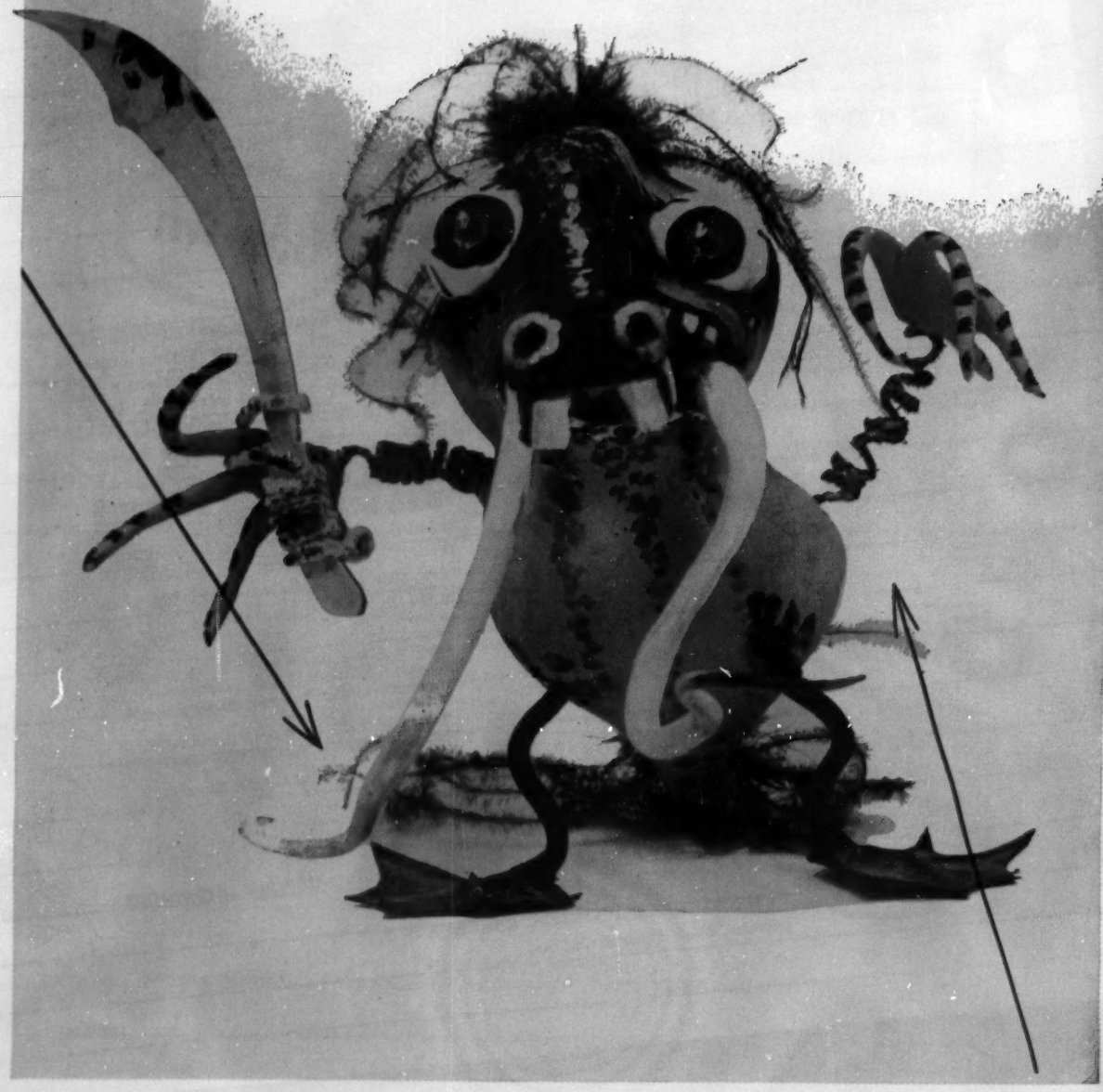

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1. Grigsby, M. E., et al., Antibiot. & Chemother., 10:1029, October, 1953.

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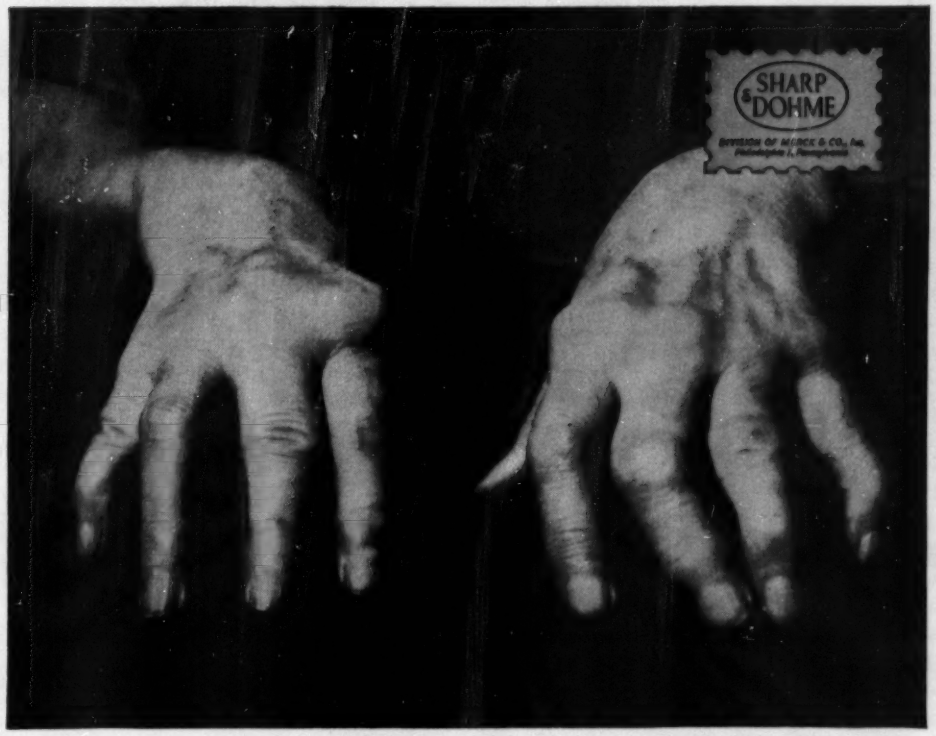

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DIAGNOSIS AND MANAGEMENT OF UTERINE MALIGNANCY

A Twenty-Five Year Experience*

GEORGE A. HAHN, M. D.,**
Philadelphia, Pa.

Cancer of the uterus is probably the most important gynecological disease, if you consider it from the standpoint of mortality. Each year 17,000 to 18,000 women die from cancer of the uterus.

The most significant factor in this is the fact that of these patients who are dying every year, 70 per cent when first seen are in the advanced state of the disease. Two out of three of the women when first treated have advanced disease already. Well, that makes the answer rather simple. The patient must be seen at an early stage. Therefore, early diagnosis must be made by (a) prompt examination, and (b) careful history-taking. Every woman should see her physician when gynecologic symptoms develop. Periodic health examinations should be done on all women; certainly all women over the age of 35 or 40 years of age.

Most women who do develop cancer do so in the menopausal or post-menopausal era. However, with our group of patients at Jefferson with cancer of the cervix about one out of three of our cases are forty or younger.

There are certain factors that are pretty well known about uterine cancer. We know that the woman who marries and bears children before the age of 20 has a greater opportunity of developing uterine cancer than the woman that marries later and then bears children. We know that the woman who bears children has about ten times the chance of developing uterine cancer as the woman not bearing children. We know that women of the Jewish race are relatively free of cervical cancer. We know that cancer of the body of the uterus is quite prone to be associated with the triad—obesity, hypertension and diabetes.

However, we do not know all that there is to know about uterine cancer. What is the earliest symptom of cancer? Well, there is no really early symptom. That is why I stress periodic pelvic examination. If there is any early symptom it is vaginal bleeding. We know, at least in our institution that 95 per cent of the patients have bleeding as a principal symptom, and in the patient in whom bleeding does not seem a major symptom, if another attempt is made at history-taking, bleeding will be found in almost every case. Unfortunately, pain is not an early symptom of uterine cancer. Where pain occurs in uterine cancer, it is either due to late malignancy for which little can be done, or it may be associated with a benign pelvic condition that happens to be present while the patient does have cancer. Vaginal discharge is not principally a symptom of uterine cancer, unless it happens to be blood-streaked. The ordinary vaginal discharge is usually due to a lacerated cervix, probably due to the trauma of childbirth. If the patient has a lacerated cervix it is a golden opportunity for repair treatment.

We do not know the cause for cancer of the cervix. However, our feeling is quite definite, that if the patient has a diseased cervix her chance of developing cervical cancer later is greater than the person having a normal, healthy-appearing cervix. And it is for this reason that any diseased cervix should be put in a healthy condition.

How does one make a diagnosis of cervical cancer? One can not make the diagnosis unless an examination is done. In other words, we need a meticulous pelvic examination and a very careful history. That is the keystone of diagnosis. And certainly, whether the man is a specialist or a general practitioner, he

*Read before the Medical Society of Delaware, Rehoboth, September 10, 1952.

**Assistant Professor of Gynecology & Obstetrics, Jefferson Medical College.

should not limit himself to a pelvic examination but an adequate general examination should be done at the same time.

Many times we have been asked "What is the proper preparation for the patient to have a pelvic examination? Patients who are bleeding do not want to be examined." Certainly, there is no preparation for a pelvic examination. If you have the patient in your office, you can examine her. Those are the important factors—the patient, the doctor, and the office.

What is necessary for the examination? You need a table, you need light, you need gloves, lubricant, and various sized specula. The diagnosis of uterine cancer is not made by any new-fangled cancer test. The diagnosis is made by pelvic examination and history.

In going over histories of patients having uterine cancer it is quite apparent that the most important single factor is the delay before which the patient reaches adequate treatment. This delay may be due to the patient. It may be that she is afraid she has cancer. It may be that she was misinformed by so-called good neighborly advice or she may have thought that any bleeding is due to the so-called "change of life."

Another factor, however, is the physician's failure to examine the patient in the presence of gynecologic symptoms; and failure on the part of physicians and patients alike, to emphasize the periodic examination of supposedly-healthy women.

There are a few things that may delay diagnosis. The giving of Estrogens or other hormonal preparations to the woman in the so-called menopausal era. Recently, in the Philadelphia area, we have heard of a so-called "premenopausal syndrome" which takes place in any woman above the age of twenty who has nervous symptoms of any type. Apparently, Estrogen is given for anyone unhappy at home or who has a tremor or a flush or what you will. If a patient is receiving Estrogen therapy and pelvic symptoms develop, the true symptoms may be masked by the medication.

In 1945 the Committee for Study of Pelvic Cancer was developed. It was formed by members of the Obstetrical Society of Philadelphia, with the sponsorship of the American Cancer Society and the Philadelphia County Medical Society. It was believed that thru the study of patients with known pelvic cancer some clue could be discovered to explain the marked delay so often present (before adequate diagnosis and treatment is instituted) in patients with pelvic cancer.

For that purpose we have two investigators who have permission to visit thirty-four of the city hospitals, and interview any patient in whom a histologic diagnosis of pelvic cancer has been made. These records are reviewed, and then once a month we have a luncheon meeting to which any doctor who has seen the patient is invited. At this time the case history as obtained by the investigator is given and then the family physician is asked to give the history, and other findings, as noted by him. There is no castigation of the family physician or anything of that type. Everything is done on a friendly plane and specialists and general practitioners alike have learned a great deal about the delay period in pelvic cancer. It has become a popular luncheon meeting-place. During the past year the average attendance has been about forty.

(Slides were then shown)

This is a slide showing the results of a 6-year period, in the Philadelphia Committee for the Study of Pelvic Cancer. There were 2418 patients studied. Of these patients having a proven diagnosis of cancer in some area of the pelvis, there was an apparent delay of 38.8%. On the other hand, when the physician was primarily responsible for delay in getting the patient to proper care and treatment, 15.5%. It was observed that the physician and patient were equally at fault in about 15%; and institutional delay occurred in 12%. Institutional delay takes place when the patient is under the care of the hospital or clinic and the diagnosis of pelvic cancer is missed or delayed. There was no delay in about 29% of the patients. In about a third the patient was at fault, a third the physician at fault or partly at fault, and a third, no delay. Here is a table demonstrating the delays according to the organ that was affected by the cancer. This table shows combined delay

on the part of the patient and the physician. Cancer of the vulva led the list, with 85%. Delay on the part of the patient diminishes with the other organs, corpus of the uterus, 65%, cervix 56%, and ovaries 52%.

I might say as far as the physician himself is concerned, physician delay was greatest in those patients having cancer of the cervical stump. In this case the delay was the fault of the physician in 58% of the cases. It is our belief that the physician is lulled into a sense of security when the patient tells him that she has had a hysterectomy. Secondly in importance was cancer of the vulva where in 50% of the patients there was evidence of physician delay.

In 1945 when the study was first originated, only about 4% of the patients had early cervical cancer. During the past year our figures show that about 23% of the patients being treated had *early* cervical cancer. In 1945 and 1946, almost 40% of the patients had far-advanced cancer for which little or nothing could be done. During the past year only about 20% of the patients had far-advanced cancer.

We definitely are of the opinion that the Committee for the Study of Pelvic Cancer has been and will be a means for reducing delay in patients with pelvic cancer.

After the history and physical examination have been done, a biopsy must be taken before any final diagnosis can be made.

Can a biopsy be taken in the office? Of course, if the doctor wishes to do one. If the doctor doesn't wish to do a biopsy, then he should send the patient to someone who will take a biopsy.

What type biopsy should be done? A spot biopsy can be done with the scalpel or biopsy punch. For patients in whom there is a diseased cervix of any consequence, in whom the spot biopsy will not suffice, we prefer doing a circular cervical biopsy. In this type of biopsy the entire squamo columar junction is removed so that a generous piece of tissue is obtained for complete histologic study. This is an ideal biopsy. It is ideal because if the patient does not have cancer of the cervix, the diseased cervix itself has already been adequately treated. We hope that adequate treatment of the diseased cervix will reduce the incidence of cervical cancer in the future.

In 1921 at Jefferson the Pelvic Cancer Clinic was developed. Since then any patient on the ward or clinic service thought to have pelvic cancer is referred to the Pelvic Cancer Clinic. Since 1921 over 700 patients have been examined in the clinic who were thought to have cervical cancer. 683 of these patients were shown to have cervical cancer, and of that group 485 patients have been followed for five or more years. The treatment we use at Jefferson is primarily radiologic in nature.

(Next Slide): We have divided the results of our treatment of cervical cancer into three major divisions, this first phase going from 1921 to 1936. These patients originally were treated with massive doses of radium and then later with a massive dose of x-ray. Some of these patients received both. Some received one; some received the other. None of them received adequate doses by present-day standards. If you look on the left side, you see the survival rates, Stage 1, we had 53% survive; Stage 2 we had about 34%; Stage 3 about 4.6% and in Stage 4 there were no survivors, for an average survival rate of about 28%. I might say between 1921 and 1926, our survival rate of all the patients treated was less than 20%. These patients did not have any planned type of treatment. The radium dose varied, the mode of application varied, the x-ray was given usually in one large dose.

From 1936 (slides) to 1942 and 1943, we had more of a plan in that all the patients received preliminary x-ray treatment, given externally, and then received a local radium application. As you see here, a little over half of the Stage 1 patients survived, 55.6%. About 34% of the Stage 2 patients survived, and then when we reach the advanced group, we observe a fall to about 8%, and again in the very-advanced stages we saved no patients. Here there has been a rise from about 28% survival to 34% or 35% average. In other words, about 1 out of 3 of the patients treated during this era survived the disease for a period of five or more years.

During the years 1942 and 1943 we evaluated our treatment and decided we should attempt a more definite plan of therapy. We instituted a practice where the patients would

receive fractional x-ray therapy first, and after a waiting period they received a local radium application in the form of interstitial needles, and capsules in the canal of the cervix and uterus. We also instituted at this time the use of vaginal cone therapy, directing the ray toward the cervix for a moderate dose of 3,000 R's (Roentgens).

These figures (slides) (1941-1946) represent the best results that we have received and here we see that about 55% of Stage 1 and Stage 2 patients have survived and 1½ per cent of Stage 3 and again none in Stage 4, for an overall survival of 47.6%. Since 1946 the trend of patient survival is about 50-55%. So if we were asked now, "What is the chance of surviving 3 or 5 years," we would say about 50 or 55%. This rise in the survival rate in patients treated with cervical cancer has not been done without a price. Because of our increased radiation dosages we have had an increase among our radiation damage. About 20% of our patients have symptoms such as diarrhea or frequency of urination and possibly bloody bowel movements or intestinal obstructions. Of these 65 patients, we had to perform 9 colostomies. We have an incidence of about 7% of fistulae. In our previous series from 1936 to 1942 we only had 2 fistulae. This is not a selected group of patients. At the present time we are working with the Department of Radiologic Physics, and the Department of Radiology to see if we can more exactly give our treatment. We feel our higher rates of survival are due to increased amounts of radiation and better applications of radium, and more intelligent management of the patients. All of our patients have a complete genito-urinary and complete bowels survey.

(Next slide): This is a comparative slide showing all the patients that have been treated who are eligible for a five-year result.

We have a few patients, 69 to be exact, in whom inadequate therapy was received. They may have had one or two x-ray treatments or possibly a radium treatment. Some had supra-vaginal hysterectomies, or had surgery of various inadequate types or inadequate x-ray in general, and we have included those patients to complete the report. As you see, in this group, we saved only 3%. So our overall five-year survival rate in all patients who have been treated in any way, at Jefferson, is about 28 to 29%. I think the figure to be remembered is the 47.6% five year survival which was obtained during the past five years, 1941-1946, by means of the planned treatment. External x-ray first, then deep Vaginal cone therapy and local radium, using capsules in the canal and needles in the cervix.

SURGERY IN CANCER OF THE CERVIX

Dr. Joe Meigs, a number of years ago, presented a notable paper on the Management of Cancer of the Cervix by Surgery, and he emphasized special criteria for those patients who should receive surgical management. Unfortunately, these criteria have not been adhered to by a good many operators, and all too often patients that have been treated surgically receive inadequate or ill-advised surgery. Surgery has varied from complete hysterectomy to complete pelvic exenteration. We believe there is a field for surgery of cancer of the cervix but surgery should be limited to institutions where the patients are carefully followed and evaluated so that one can at a later date properly evaluate the results of the treatment of cancer of the cervix by means of surgery.

For about three years at Jefferson we have been performing extra peritoneal iliac lymphadenectomies. We haven't done enough to know what the final results will be. In about five years we hope to be able to tell you whether that particular type of procedure is worthwhile. At any rate, we definitely believe that the average patient with cancer of the cervix should have the benefit of treatment by irradiation. In our institution we believe that the average patient has an opportunity for a 50 to 55% survival if treated at this time.

During the past few years other types of treatment have been used, such as supervoltage x-ray therapy, irradiated colloidal gold, and Cobalt-60 as well as various other isotopes.

At the present time the diagnosis of uterine cancer, particularly cancer of the cervix is still made by history-taking, pelvic examination, the biopsy of the cervix and periodic health examinations.

The type of therapy which we prefer is irradiation and we believe that about a 50 to

55% five year survival rate should be expected in any patient with cancer of the cervix treated at this time.

255 S. 17th Street.

DISCUSSION

DR. J. F. HYNES: (*Wilmington*) Mr. Chairman and Members of the Society: I was very much interested in Dr. Hahn's paper which I think shows some very fine results.

I think he does himself an injustice by reporting the cases from 1921 to 1926, etc., because we all know that the treatment in those years was quite inadequate in everybody's hands. It is only in the more recent years, particularly with the development of the higher voltage x-ray tubes and with the knowledge of measuring radiation, that it is or has been possible to give anywhere nearly adequate or even uniform treatment to patients.

My own experience is not as extensive as his. We have had over the past 15 years or have seen, about 550 cases in Wilmington, at the Memorial Hospital. Most of them, or at least some of those of course are too recent to know what the results of treatment will be. Of those patients, some of them are not really suitable for analysis, in that they represent patients that followed other clinics or were treated elsewhere, and came in to us for treatment of metastasis, or something of the sort. And our survival rate is about the same as Dr. Hahn's here, as reported—around 50%.

I think that there is one very definite change in the case material over the past years. A good many years ago I worked out figures on the question of delay on the part of the patient, and delay of the doctor, before getting the patient to adequate treatment, and it ran to a good many months. I think that is no longer the case. There are few patients where the doctor is responsible for the delay in getting the patient to be treated and, for the reason we are seeing the patients in the early stages of cancer of the cervix the results are improving.

I am not sure our treatment is very much better, that is, within the recent period, but I am quite sure we are seeing more patients where they have an opportunity of cure.

The question as to the treatment to be used comes up. Ten years ago it was pretty well settled—they were all treated by radiation. Now there is a question whether surgical treatment may not be better. Various reasons are advanced for the advisability for surgery, such as the freedom from post-radiation complications, the possibility of later recurrence, and later radiation complications or changes leading to a radiation cancer, even. That has been brought up by Meigs, particularly. My conviction is the same as Dr. Hahn's, that is, we still find radiation therapy the best way of treating carcinoma of the cervix.

We have had in this group about 8 or 10 patients requiring colostomy. We have had two or three vaginal fistulae that had to be repaired, and others with the progressive disease where nothing could be done about them. However, it seems to me that surgical treatment by total hysterectomy, no matter how wide, is still a pretty limited operation, when dealing with the uterine cervix, because you can't give it very much margin.

If surgical treatment is necessary for a patient with cancer of the cervix and particularly with a patient with recurrence after unsuccessful radiation, then there probably is a place for pelvic evisceration. I don't know the exact number of cases that have been done, about 25 or 30. The mortality has not been too bad; it would run in the neighborhood of 20 per cent. And there are a number of patients who are apparently well. No patients have survived for five years, as yet, and there have been a number of deaths from recurrent cancer. But it seems to me there is a place for that operation in certain selected cases.

I mentioned that there was a definite improvement in the results obtained in the last five years. I feel that is primarily because we are seeing them sooner.

It looks as though the survival rate will be in the neighborhood of 60 per cent.

DR. O. N. STERN, (Wilmington): I think this is a timely paper. I at first had some thoughts of discussing this in the light of 74 cases which I have treated personally since 1946, since my return from the army. However, there is another side to the paper that I think is more to be emphasized; that is, the matter of the examination of the person.

We all have sent Pap. smears away that have come back positive; have taken the

patient to the hospital, and done a D and C biopsy and have gotten negative results. Then we have repeated the Pap. test and have gotten a positive result. What should we do in these cases? There are reports in which the two Pap.'s had been done and biopsy and curetage disclosed nothing—but in view of the fact there had been positive Pap. nodes and they had been repeated, a laparotomy was done and a carcinoma of the tube was found. I think we should be very cognizant if the Pap. is taken right, and even though they get negative findings on the curetment and biopsies, I think the patient should be carefully watched, if necessary, at a later date, explored.

Next is the cervix of the pregnant woman on examination. All of us are cognizant of looking at the pregnant cervix and finding erosion is quite marked and which on occasion can bleed on touching. I think all these cervices enduring pregnancy should be biopsied even on a tendency toward viability; seeing by pressure against the area whether or not increased bleeding can be obtained. The bleeding which comes from your biopsy can be controlled with Jelu-Cel or one of the other oxidized gauzes. I would like to emphasize this biopsy because in the city of Wilmington, in the last ten years, we have had three cases of carcinoma of the cervix complicating pregnancy.

Recently, at one of the hospitals a carcinoma was picked up. This patient was hysterectomized because near term, and treated with radium. As far as I know—and that is about a year ago—that patient is well and healthy. But we should not lose sight of the fact that frequently during the course of pregnancy, even though the cervis can take on various simulating pictures, and cancer should not be forgotten.

I would like to close with an interesting case that most of us in Wilmington are acquainted with. A young girl whom I saw in December, 1949 had been up to the Harvard Medical School because of a severe valvular lesion, for operation, because of an old rheumatic disease. While up there a superficial examination was made of her genital system and pelvic examination was not made. She was operated on successfully. She came back to Wilmington and started bleeding. I did a biopsy, to find she had an epidermal cancer of the cervix. No speculum had been used originally, no pelvic had been done, and the Pap. had been done by a swab and stick, and in that way only, and sent to the lab. I think this is an illuminating case and should put us all on our toes to watch when doing the pelvics, that they are properly done under proper illumination.

DR. E. Y. GLEDHILL, (*Wilmington*): Dr. Hahn spoke of the increase in radiation reactions and damage in the result. I would like to ask him if there has been effort to correlate that with the extent of the disease, recognizing that sometimes when you destroy the cancer that is invading the floor of the bladder that you can't help but produce such a fistula.

DR. CHRISTENSEN, (*Salisbury*): I am somewhat interested in total radiation dose and the plan of x-ray and how you decided to settle on preliminary x-ray and post-radium x-ray. I am also interested in the change of radiation damage figures from the earlier series to the latest series, and what conclusions you have come to about that.

And then in connection with that, I would like to get Dr. Eisenstein to show two of your slides over, with respect to the effectiveness of treatment.

(Showing the slide referred to) Now this is a series of five-year results in the group of patients treated in the period 1942-1943 and to 1946, and I call your attention particularly to results in League of Nations Stage 2 patients and Schmitz'. Now, let's look at the other group. If you will compare the results in the League of Nations' Stage 2, here and Stage 1, here, if you can remember them, 55 and 34, roughly, and 55 and 55, roughly, it seems to me that there may be something there that suggests that it is not "cricket" to increase the radiation of the Stage 1 League of Nations' patients and suffer the increased radiation damage.

There has been shown definite relationship between radium dose time, equivalent, and radiation damage and I would like to know whether your experience has been similar—that is, that a similar total millicuries or milligram hours of exposure obtained with a

smaller dose of radium over a longer period of time, as opposed to a large application of radium applied over a less period of time, with a distinct diminution of radiation damage.

For a group of gentlemen interested in treating patients that go home, I thought maybe you might say something about the importance of careful follow-up and the salvage in follow-up patients with recurrences because I think that is a palpable and important figure and should not be overlooked.

I am interested in how you are getting along immediately, as far as your radiological damage in the lymph adenectomy group as opposed to those in the ward group. Last, I would like to give a little bit of credit to Mrs. Graham because I think a very remarkable piece of work has been done with a Pap. stain in her hands, especially in the group of patients—where radiation is going to fail, and call your attention to the fact that it may not be too far in the future when, with the aid of vaginal smear, we can separate and predict the radiation failures. She has been able to demonstrate that in a group that she considered as inadequate radiation response about 97% of the patients failed to survive, whereas in the group of smears taken after, or during, or well into the radiation treatment she was able to demonstrate where she called it an adequate response, the rest of the patients fell, and of course there was a considerable mortality in the group, anyway. But when she said the radiation was inadequate, the patients died. That is just interesting from the standpoint of those treating the disease.

DR. H. W. SMITH: (*Harrington*) I had a question in mind and Dr. Stern has touched upon it briefly. I would like to ask what the general practitioner can expect of the positive Pap. smears as related to diagnosis of carcinoma of the female genital tract.

DR. HAHN: I will preface my remarks by saying if I could answer all these questions completely it would be a complete course in gynecology.

In regard to some of Dr. Hynes' remarks, I do feel that there is less delay now in the patient getting to treatment, and that is evidenced on our charts. In the last chart very few Stage 3's and many more Stage 1's and 2's are noticeable, whereas in the earlier charts the reverse was true. As to pelvic exenterations, we have not done any at Jefferson, but in other institutions the primary mortality rate is from 20 to 40 per cent. If your mortality rate is less than that you are to be congratulated. Pelvic exenteration is an extensive operation which may give five to ten per cent survival. I agree, it may be indicated occasionally but I think one should study the patient most carefully, before subjecting her to that type of surgery.

Now, Dr. Stern, in regard to the Papanicolaou smear, and the examination of the patient: I have a slide. I didn't know originally that we were going to talk of Papanicolaou Smears, but it might be interesting.

(Slide): I think this may also answer in part Dr. Smith's question. These 96 patients had or were known to have cancer of the cervix before treatment. All had smears taken, not only from the cervical canal, but from the posterior vaginal fornix and aspiration of the cervical canal up. We had 10% false negatives. (Referring to slide). These are known cases of cancer of the cervix.

We feel the Papanicolaou smear is a valuable screening test, but the most important factor is the physician. If the doctor is suspicious of cancer and the Papanicolaou is negative then a biopsy and/or D & C should be done. It all comes back to the physician. He is the most important single diagnostic factor in pelvic cancer.

In regard to the pregnant woman, we certainly have no hesitancy in taking a biopsy in a pregnant woman, with a suspicious cervix. Dr. Murphy in our department reported 50 consecutive biopsies taken on pregnant women with no untoward complications.

I was interested in what Dr. Stern said and I think his report emphasizes the pelvic examination as being part of the routine examination.

Dr. Gledhill, unfortunately it is true that the patients receiving the most radiation damage were in the earlier stages.

Dr. Christensen asks the total radiation dose or what is planned. Our dose plan is 2400 roentgens. The average field is 10 x 14 cm. and the filtration is one-half mm. cop-

per and one mm. aluminum. Seldom do we go below that dose. Sometimes we increase it. The external therapy is directed perpendicularly into the abdomen not cross-firing the cervix. We then apply 3000 roentgens through the vaginal cone, using the largest cone the patient will tolerate, and direct the ray to the cervix. The radium is given as I mentioned before by intra cavitary and interstitial radium, using 100 mg. each for average dose of mg. hours of about 5,000.

We give preliminary x-ray therapy first since it stops bleeding, reduces ulceration, and infection, and reduces the lymphatic extension of the disease.

In reference to the figures in the 1936 to 1942 and the 1942 to 1946 grouping, Dr. Christensen asks the advisability of increasing the stage 1 irradiation which was similar to the question Dr. Gledhill mentioned. Our plan of treatment was designed in 1942 and 1943 and originally in 1936, to be a treatment which should be given according to plan. And we have carried on with this plan. In the light of the increased radiation damage, I admit the Stage 1 and some Stage 2 cases have shown a greater amount of damage.

In regard to the work that Dr. Christensen mentioned, we are not willing to use a very small amount of radium for a prolonged number of hours. We do not believe there is enough evidence to change our technic as yet.

In regard to the follow-up of patients with recurrence, about six years ago a paper was presented on the re-irradiation of patients treated with cancer of the cervix, and I believe we had about an 8 per cent salvage in patients who had been re-irradiated. As to the lymphadenectomy patients, we have had no bad results as yet.

The Papanicolaou work done by Ruth Graham was mentioned. We are not able to duplicate her exact results. However, we are continuing that work. Dr. Rakoff, whom some of you may know, is an able cytologist, and we hope to be able to get a better correlation between radiation-sensitivity lesions and radiation-resistant lesions, but so far we have not been able to utilize the results in any practical way.

DRUG THERAPY IN THE MANAGEMENT OF HYPERTENSION*

CHARLES LEVY, M. D.**
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A favorite subject in the medical literature today is the treatment of hypertension with new medicinal agents. Many new drugs have been under investigation by medical research teams and several of proven merit have been reported. Some cause a lowering of blood pressure in hypertensive disease by producing what has been labeled a medical sympathectomy; others exert effects reflexedly or through central or peripheral action. Familiarity with the mode of action of these new agents, and thorough knowledge of the side effects, are absolutely necessary in order to properly understand the place of these new drugs in our medical armamentarium.

Before treatment is instituted, a thorough study of the patient must be made to ascertain if possible the etiology of the hypertension. Of the known causes, which number about 5% of the total number of cases of hypertension, are included: pheochromocytoma, Cushing's disease, coaretation of the aorta, unilateral kidney disease, toxemia of pregnancy, and acute glomerulonephritis. It is then essential to determine the status of the cerebral, coronary and renal vessels as producing hypotention in cases where degeneration of these structures is present, may result in precipitous catastrophies.

Many patients with hypertension are asymptomatic and may go on for many years without serious damage developing in any organs; some cases, on the other hand, suffer serious trouble early in the course of their illness. As an illustration of the asymptomatic hypertensive, I followed a patient, Mrs. M. E. B., age 77, in my office whose blood preessure was 300/140. She remained quite comfortable under symptomatic therapy of hypertension for 5 years and then developed congestive heart failure and died.

The question of when to treat is a good one. Many cases require only reassurance and guidance. Meilman[1] feels that the elderly patient who has had a long standing history of hypertension and who does not show evidence of

*Presented at Joint Staff Meeting of Wilmington hospitals at Wilmington General Hospital, September 22, 1953.
**Chief in Medicine, Wilmington General Hospital.

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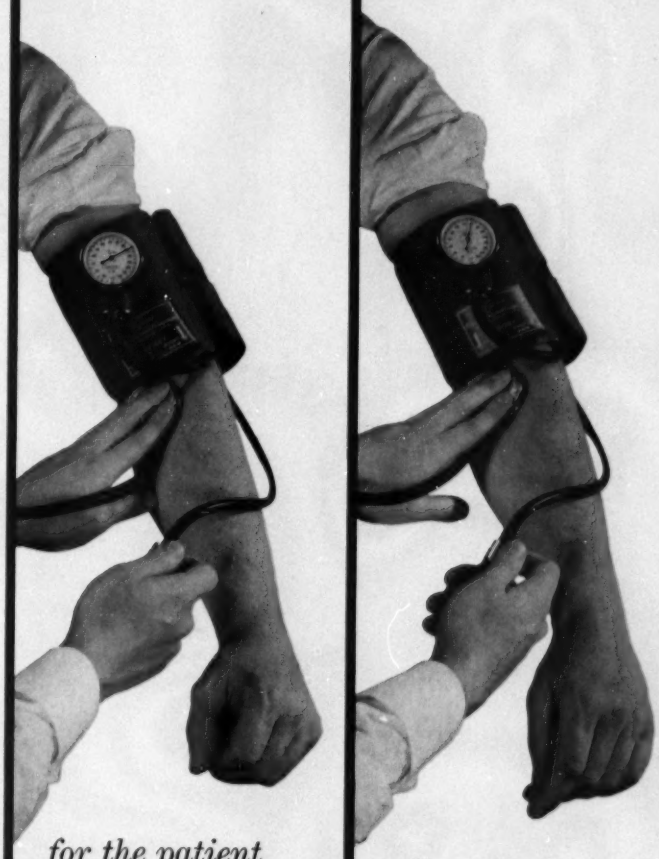

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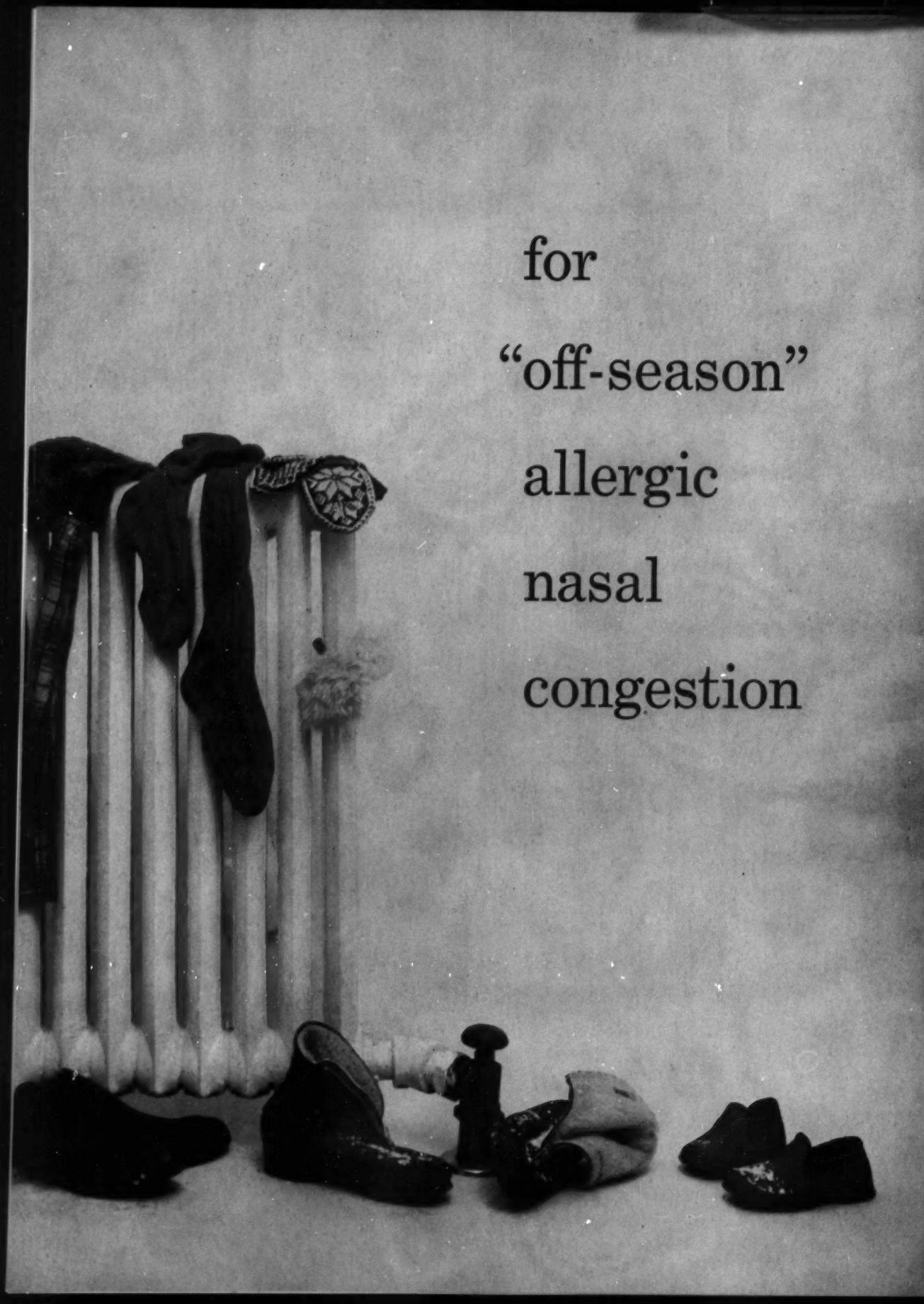
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hypertensive cardiovascular disease is better left free of dietary and drug restrictions. Young individuals, with no symptoms or signs other than high blood pressure, usually require only supportive psychotherapy to prevent development of hypertensive neurosis. On the other hand, it is a known fact that hypertension increases cardiac load, accelerating the onset and accentuating the development of arteriosclerosis. To lower the high blood pressure to more normal levels may delay the progressive development of hypertensive cardiovascular disease and arteriosclerosis.

In the treatment of hypertension we do recognize several methods with distinct value and frequently a combination of these methods may be of benefit in the treatment of the individual patient. The value of rest is recognized. Psychotherapy, sedation, low salt diet, drugs, and finally sympathectomy or sympathectomy with adrenalectomy—all have their advocates. Wilkins[2] presented a beautiful outline of the drug therapy of hypertension and gave an excellent review of their indications with case reports.

GANGLIONIC BLOCKADE

Hexamethonium produces adrenergic blockade at the level of the ganglia. Hexamethonium, or C6, is a quaternary ammonium compound which is a powerful autonomic ganglionic blocking agent. It effectively blocks the transmission of nerve impulses acting at the ganglionic synapse in both the sympathetic and parasympathetic systems. It produces a marked and a relatively prolonged hypotensive effect. It must be used with extreme caution as it is a potentially dangerous drug. The effect of this agent may vary from patient to patient and tolerance to it develops rapidly. It is slowly absorbed from the gastrointestinal canal, and only about 5% enters the general circulation. Because of this, constipation must be avoided and a laxative should be given daily. The patient receiving this drug must always be under close supervision. In the presence of impaired renal function extreme caution must be exercised as the drug may accumulate in the blood stream to high levels. Vascular thrombosis is a danger and may result if prolonged hypotension is produced in patients with coronary or cerebral vascular disease.

A fall in blood pressure with marked postural hypotension is the chief effect of the drug. Side effects are as follows: blurred vision, tachycardia, dry mouth, nasal stuffiness, nausea, heart-burn, urinary retention and constipation, which may progress to paralytic ileus. As hexamethonium may increase the sensitivity to pressor agents, adrenalin is contra-indicated. In extreme hypotension, the head should be lowered and vasoxyl (methoxamine hydrochloride) or neosynephrine (phenylephrine) should be used.

Hilker[3] reported on 30 cases with a response which was declared variable. Seventy-two percent (72%) of his cases developed postural hypotension, but is was difficult to maintain a constant lower pressure. Moyer[4] reported results on 120 patients to whom he had prescribed hexamethonium on an out-patient basis. He reported excellent results, as all but 17 of his cases responded with a reduction in blood pressure, and with improvement in signs and symptoms of heart failure, improvement in P.S.P. excretion, and improvement in papilledema.

Smirk[5], and his co-workers, in a study of 130 patients also reported excellent results. Some of their patients have been maintained for 12 months or more on C6. Sokolow[7] reported his results on 17 cases of malignant hypertension in which he declared that the prognosis was no longer hopeless. He noted clinical improvement in 10 of his 17 cases with a reversal of the papilledema. In the report offered by Moyer, Snyder and Johnson[8] of a study of 58 unselected ambulatory cases with moderate to severe hypertension, they reported all but eleven were benefited by hexamethonium. The administration of a presoline in combination was used for the control of eleven of eighteen additional patients who were not adequately controlled with hexamethonium alone. The ganglionic blockade produced by hexamethonium does not alter the (sedative) vasopressor effect of apresoline. It does block, however, at least part of the tachycardia and the increased cardiac output. Klayman, Silberg and Karlen[9] describe a fatal case that followed hexamethonium administration. Paralytic ileus and shock developed in their patient. This case report with references to 5 other deaths which were re-

ported in recent literature, all due to hexamethonium, was presented. This again emphasizes the importance of a full knowledge of the pharmacodynamics of this potent drug before its use.

ERGOT ALKALOIDS

The dihydrogenated ergot-alkaloid is an example of the centrally acting group of drugs, which are also adrenergic-blocking agents. Hydrogenation was shown by Stoll[10] and his co-workers to alter the activities of some of the ergot-alkaloids. Hydrogenation alters the usual vasoconstriction effect and the ability to stimulate smooth muscle and, in addition, it increases the adrenergic blocking activity of the ergot-alkaloid. Hydergine contains a mixture of three hydrogenated alkaloids of the ergotoxine group: dihydro-ergocornine, dihydro-ergocristine, and dihydro-ergokryptine. Pharmacologically the drug produces: (1) a central sedative action (inhibition of the higher vascular centers); (2) lowering of vascular tone; (3) a direct peripheral adrenergic blockade; and (4) centrally induced bradycardia.

The drug also produces nasal congestion and postural hypotension. At times fatigue and listlessness. Occasionally there is nausea. Hydergine must be given parenterally but the patient can be taught, following standardization, to give it to himself like insulin. The drug frequently produces sufficient subjective improvement, and is sufficiently safe to be of value.

HYDRALAZINE

Another example of centrally acting drugs is 1-hydrazinophthalazine, sometimes referred to as hydralazine, or under the trade name of Apresoline. The effect of this drug is chiefly central but it has no sedative component. It does lower both the systolic and diastolic blood pressures. The action is apparently in the mid brain with the result that an excessive out-flow of sympathetic vasopressor impulses is prevented. The drug also exerts a moderate degree of adrenergic blocking action against the pressor effects of adrenalin. The drug causes postural hypotension, tachycardia and headache. In addition, other side effects are weakness, dizziness, nausea and vomiting. Less common are numbness of the extremities and nasal congestion. The headache which Apresoline causes is of the histamine type and may be due to the suppression of histaminase. An important effect is an increased renal blood flow. By increasing the blood flow through the kidneys, hydralazine tends to interrupt the vicious cycle of renal ischemia, with its attending release of pressor agents. Apresoline reduces cerebral vascular tones but cerebral blood flow is not decreased in spite of the fall in blood pressure. One is cautioned in the use of Apresoline in coronary cases where a reduction in the blood pressure may be hazardous as there is increased cardiac output in addition to tachycardia.

Hilker[3] reports a significant fall of systolic blood pressure in 66% of his cases; and a fall of 44% in the diastolic blood pressure. The combined use of hydralazine with hexamethonium has been recommended by Schroeder[6]; whereas Hilker stated that the combined therapy offered little advantage over the use of hexamethonium alone. Paige commented that he was against such polypharmacy. Schroeder reports some apparent late toxicity of the drug: (1) 5 cases of acute interstitial fibrosis of the lungs in a series of 258 cases; (2) 2 cases which resembled disseminated lupus; (3) 5 cases which developed rheumatoid arthritis, probably due to Apresoline.

Kauffman[11] reported a case of pancytopenia in a recent Journal of the American Medical Association. Moser[12] reported a case of acute psychosis due to hydralazine therapy. The report deals with a patient who experienced a severe psychotic episode due to an overdosage of Apresoline.

DIBENAMINE

Dibenamine is a peripherally acting drug which is sympatholytic in action, acting directly and preventing the smooth muscle of arterioles from responding to vaso-constrictor influences. Dibenamine has its disadvantages as it must be given in a slow drip intravenously. The side effects are restlessness, drowsiness or confusion. It has not been recommended for routine use but it has been used to tide a patient over an acute episode.

A new long acting peripherally effective adrenergic agent which has been recently synthasized is dibenzyline. Its action is much shorter than dibenamine. It produces a marked fall in orthostatic but only a moderate fall in

supine blood pressure. It can be given orally. It blocks the pressor effects of circulating adrenalin, acting at the nerve endings in the blood vessel walls. The side effects are nasal stuffiness, dryness of the mouth, miosis, postural hypotension, tachycardia, drowsiness, fatigue and rarely nausea and vomiting. The chief disadvantage is the tachycardia. Miller[13] compared the results in the use of this agent with results in a group of patients treated with other newer drugs. Eleven of 23 patients were benefited with dibenzyline. Miller[13] declared that in his opinion hexamethonium was the drug of choice.

VASODILATORS

The nitrites are quite well known as vasodilating drugs with action directly on the blood vessel wall. It has been suggested that the drug partially counteracts the predominant sympathetic vascular tone found in hypertensive disease. The nitrites have little effect on the blood pressure except of course nitroglycerine with its particularly short period of action. An unpleasant side effect is the headache that accompanies its use.

VERATRUM GROUP

The veratrum group of drugs acts centrally. The mode of action is unknown but it does act upon the central nervous system and the vagus, producing vaso-dilatation. It produces a reflex fall in blood preessure and slowing of heart rate by afferent stimulation[41] to vasomotor centers through central vaso-depression. There is a resultant decrease in peripheral resistance which is not accompanied with a reduction in cardiac output. Unfortunately, however, there is a narrow range between the therapeutic and the toxic dose and there is a great variation in the dosage requirements of individual patients. Veratrum causes nausea and vomiting, salivation, tight throat, paresthesia about the mouth, tingling of the hands and feet, severe hypotension, even collapse and bradycardia. This bradycardia is of vagal origin and can be prevented with atropine. Veriloid contains a mixture of active hypotensive esters of veratrum viride. The bioassay method[15] utilized the property of the drug to block the carotid sinus pressor reflex.

A new preparation of veratrum pure esters derived from veratrum alba has been declared superior to alkaloid of veratrum viride in that it produces less nausea. Veratrum is a liliaceous plant native to Europe. Protoveratrine A and B are the active purified esters from this plant. A principal advantage is that a dosage of the drug is based on weight and not on bioassay. Hoobler[16] states that this drug is superior to Veriloid and it is useful in patients with heart failure as it may reduce the blood pressure and slow the heart rate without lowering the cardiac output.

LOW SALT DIET

A method recommended many years ago for the reduction of high blood pressure is the low salt diet. Allen[17], in 1920, originally propounded the value of salt restriction in hypertension. Corcoran[18] and Watkins[19] reported effective results with the use of low salt regime. In 1944, Kempner[20-21] reported excellent results with the rice diet with its very severe restrictions, limiting the diet to rice, fruit and sugar. The excellent results claimed by Dr. Kempner to be due to his rice diet have been questioned, and many feel that the hypotensive effect of the rice diet is due to its low sodium content. A low salt regime is frequently used as adjunctive therapy to drug and other methods of treatment.

THIOCYANATES

The use of thiocyanates was in vogue quite a few years ago. Its action is still not truly known. It may have a slight sedative action and it may also have some vaso-depressing effect on the smooth muscle of arterioles. Toxic reaction such as psychosis and dermatitis are frequent and it is imperative that the blood level be followed. A blood level of 8 to 12 mgm.% is recommended. Unless there is good kidney function, an excessive level may occur with the toxic reaction. Cyanate goiter, occasionally seen, is due to blockage of the formation of thyroxin by thiocyanate.

PYROGEN

If there is good renal function intravenous pyrogens have been suggested in the treatment of hypertension. It causes a general and a special renal-vasodilatation. The treatment with pyrogen is still in the experimental stage and is not particularly recommended as it is a very rigorous form of therapy. Taylor[22] and his group in a report in the use of Pyromen, which is a water soluble pyrogen, noted

improvement in some cases but this improvement was not maintained.

RAUWOLFIA

Finally, a drug which is a native plant of India and used as a root or powder (Rauwolfia-Serpentina) has been introduced. It is trade marked as Raudixin, a whole extract, by Squibb or Rauwiloid, a purified alkaloid by Riker. The drug is well tolerated and is effective in about 50% of the cases. The drug has been recommended because of its almost universal absence of side effects. Its action is on the central nervous system, is slow and requires 3 to 5 days to several weeks for the maximum effect to be noted. Wilkins and Judson[23] declare the drug is well tolerated. They feel that the drug produces its effect through some sedative action. It produces subjective improvement with a type of emotional calm. The drug, because of its distinctive bradycardia, which is not blocked by atropine, can be used to good advantage in patients who are also taking veratrum or hydralazine[23] The drug causes nasal congestive, bradycardia, a sedative-like action, a slight laxative action and may promote weight gain.

SUMMARY

Drug therapy in hypertension is certainly not the last word. Some of these drugs are beneficial but at the same time have certain serious drawbacks. Certainly, before the use of any of the agents a complete physical survey of the patient must be done. The advantages and disadvantages of the drugs under consideration must then be weighed. A close supervision over each patient must be maintained as each patient may react differently. Hospitalization for study prior to use of these drugs is certainly advisable. The effect of stressful situations and emotional conflicts cannot be overemphasized. Therapy should be withheld from patients with serious coronary atherosclerosis, brain, or serious kidney disease due to the danger of vascular thrombosis when the blood pressure has been lowered. At times combinations of drugs may be advisable, utilizing the favorable effects of certain agents as (1) the renal vaso-dilatation of Apresoline; (2) the bradycardia of veratrum; (3) the sedative action of Rauwolfia. Drug therapy is a step forward but its ultimate value will await the test of time.

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THE DIAGNOSIS OF RENAL TUMORS*

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The diagnosis of renal tumors is sometimes an easy thing and sometimes most difficult. In the vast majority of cases the initial warning comes as the presence of blood in urine. This may be gross or microscopic, but is usually of a painless nature, the complaint being that the patient sees blood in his urine but has no distress. At times the initial complaint is of a mass in the side. These tumors are usually large and present the problem of difficult surgical removal and small hope of cure. At other times there may be a dull pain

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in the right or left flank which leads to urological study and incidental discovery of a tumor. An aid to diagnosis is an examination of the centrifuged urinary sediment after staining by the Papanicolaou technique. The diagnosis of renal tumors is eventually made by x-ray examination of the urinary tract, either by intravenous urography or retograde pyelography. Cystoscopy and the retrograde pyelogram give the clearest pictures and best evidence. A new aid in the diagnosis of renal lesions is translumbar arteriography, with the injection of radio-opaque dye directly into the lumbar aorta. This technique is of particular benefit in differentiating large solitary cysts of the kidney from renal tumors.

In the following series of lantern slides I would like to show different cases which illustrate the various problems in a diagnosis of renal tumor.

This first slide is a characteristic picture of the filling defect and spider web deformity of a renal tumor. This was a 55 year old white female who complained of gross painless hematuria. Nephrectomy was performed by the Nagamatsu technique.

These next two slides are of large renal tumors, each weighing over 1800 grams, which caused no symptoms at all until a mass in the side was discovered at routine physical examination.

The diagnosis of renal tumor is often confused with cysts of the kidney, either solitary or polycystic disease. In this case the impression on intravenous urography was of polycystic disease but retrograde pyelograms gave a more complete filling of the renal pelvis with a more pronounced localized filling defect at the upper pole, and the preoperative diagnosis was renal tumor at the upper pole. At operation multiple cysts of the right kidney were found and ruptured.

This next case is an example of too much medical care. A young man of 26 years with two bouts of gross painless hematuria. At cystoscopy blood was seen coming from the right ureteral orifice. He was observed for several months, during which time he had more or less constant dull right flank pain and 20 pounds weight loss. Retrograde pyelography revealed a deformity in the lower major calyx of the right kidney, which could be described more as a fuzzy irregularity. It was thought that we might have here a very early renal tumor. Right nephrectomy was done; the pathological diagnosis showed no evidence of tumor but papillitis of the lower major calyx.

As with so many medical situations there is sometimes no rhyme or reason in the course of renal tumors. This 40 year old white male had a mass in his side and was operated upon for an intestinal complaint. Intravenous urography had been done and was considered normal, yet at operation there was a large retroperitoneal mass in the right upper quadrant with widespread metastatic carcinoma throughout the abdomen. Biopsy of this mass revealed hypernephroma (clear cell carcinoma of kidney).

This man whose slide you saw before with the huge mass in his side the size of a football is now well and happy, working every day, and it has been two and a half years since his nephrectomy.

In closing I would like to illustrate some of the unfortunate results of complacency and carelessness, both on the part of the physician and the patient.

One case is of a 48 year old colored man who had gross painless hematuria three years before nospital admission. He went to a neighborhood drug store and got some pills, which promptly cleared his hematuria. He returned to the hospital three years later, again with gross hematuria and a massive tumor filling the right upper quadrant. At nephrectomy, a large tumor of the lower pole of the right kidney was discovered which had broken through its capsule and was plastered to the retroperitoneal area. He died three months after nephrectomy.

A second case is of a man who had intermittent hematuria over a period of two years and did not report it to any physician. On routine physical examination a large mass was discovered in the left upper quadrant which on study proved to be a massive clear cell carcinoma of the kidney. Nephrectomy was done by the Nagamatsu technique but he died within six months of extensive metastasis.

This final case is of a white female aged 55 who is at the present time in the hospital. At nephrectomy (transperitoneal) a large tumor

of the left kidney was present. There was tumor tissue growing down into the renal vein and fastened to the aorta and entire retroperitoneal space. Last July (nine months before present hospital admission) she had had gross painless hematuria but so confused her physician with an indefinite story that a diagnostic D & C was done and nothing was found It was felt that she had uterine bleeding from some hormonal imbalance and it was not until a second bout of gross painless hematuria nine months later that urological study revealed this large tumor mass.

PATHOLOGY OF RENAL TUMORS*

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In my medical school "Text Book of Pathology," Boyd's 1934, I found his initial statement about renal tumors to be that "there is no more perplexing chapter in pathology than that dealing with tumors of the kidney." He proceeds thereupon to deal with this subject in merely three and a half pages. He classifies tumors in four types: (1) the Grawitz or hypernephroma; (2) the Wilms' embryoma; (3) benign tumors, such as fibromas, adenomas hamartomas and (4) sarcomas and villous papillomas.

Our concept as to the pathology of renal tumor has shifted in the past 20 years to a clearer tumor classification, even though we are discussing basically the same tumors. Allen in his most recent monograph on the kidney (1951) devotes 80 pages to tumors of the kidney. His classification is much more extensive and complete and will serve our purposes better, since we have more than a few varieties to present later in the clinical side of tonight's presentation.

According to Ackerman and Regato approximately 99% of all solid renal tumors are malignant, and 80% of these are adenocarcinoma. These occur most frequently in men 46 to 55 years of age, and 10 years earlier for women. In a series of 402 cases collected by Albarran, 227 were in males and 175 in females, the left kidney involved more than the right in a ratio of 6 to 5. Neoplasms of the kidney pelvis make up only 5-10% of all renal tumors. Again, Albarran in a series of 585 kidney tumors found only 42 originating in the renal pelvis. Wilms' tumors make up about 6% of all renal tumors; 80% of these occur under the age of 7, and very few after the age of 15. Campbell in his "Pediatric Urology," discussing malignant renal tumors, states that *carcinoma* of the kidney is most rare in the young, some ten cases having been recorded to date. The Wilms' tumor is the *usual* renal neoplasm of early life and comprises 20% of all tumors in children, and is found in approximately one of every 1500 children admitted to a pediatric service. *Here* there is no predilection for one kidney or the other, or for one sex or the other. This differs from adult carcinoma but corresponds to the observation made on other congenital lesions.

The over-all data regarding renal carcinoma in its relation to other cancers indicates that renal cancer constitutes approximately 1.3% of all cancers, and is more frequent in males than females. Benign tumors are found in about 5% of kidneys.

CLASSIFICATION OF RENAL TUMORS (ALLEN)

Benign

Cortical (tubular adenoma)
Solid
Cystic
Fibroma
Lipoma
Myxoma
Angioma
Lymphangioma
Hemangiopericytoma
Leiomyoma
Mixed tumor with combination of above elements: Angiomyolipoma, myxolipoma, etc.
Dysontogenetic rests
Adrenal cortical rests
Chondral and osseous rests
Dermoid cysts
Endometrioma

Malignant

Adenocarcinoma (tubular) Garwitz tumor; hypernephroma
Wilms' Tumor
Fibrosarcoma
Liposarcoma
Leiomyosarcoma

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Angiosarcoma and other compounded sarcomas

Metastatic tumors—Leukemia—Hodgkins

Tumors of the Renal Pelvis

Papilloma

Papillary transitional cell (epidermoid) or squamous cell carcinoma

Non-papillary transitional cell (epidermoid) or squamous cell carcinoma

Mucous Adenocarcinoma

Tumors of the Renal Capsule

Fibroma

Lipoma

Angioma

Leiomyoma

Myxoma

Tumors with combinations of the above elements and their malignant counterpart.

Except for the parenchymatous adenocarcinomas, the pelvic papillomas and the Wilms' embryoma, the others are either oddities or relatively insignificant from the clinical point of view.

CELLULAR PATHOLOGY

A. Renal Adenocarcinoma. It is now reasonably clear that this neoplasm, with possibly rare exceptions, arises from the tubular epithelium, usually beginning as an "adenoma," rather than from adrenal rests residing within the parenchyma of the kidney. The qualifying terms granular cell, clear cell, spindle cell or hetero-cellular adenocarcinoma now often appear artificially and insignificantly distinctive.

The primary renal carcinoma is found in any portion of the parenchyma. It may be three cm. in diameter and lie solely within the cortex, or may grow as large as one reported weighing 3300 gms. These tumors are usually spherical or bosselated, and moderately soft. On section they are bright yellow and, especially in the larger tumors, mottled with deep red hemorrhagic and necrotic areas and gray areas of fibrosis. The smaller tumors appear deceptively encapsulated. The larger ones invade the adjacent parenchyma and pararenal tissues and showing particular propensity for entering the renal vein and extending in continuity up the inferior vena cava to the right heart. (Allen, plates 285 to 294 illustrating renal adenocarcinoma). The cells frequently resemble tubular epithelium. Some of the tumors are made up of clear cells with small uniform nuclei and cystoplasm containing lipid with vitamin A. The vitamin A is demonstrable with fluorescent microscopy. Other adenocarcinomas have clear cells mixed with granular cells, and still others have components of virulent spindle cells that are truly altered cancer cells, but may be mistaken for sarcoma or a varient of Wilms' tumor. The patterns are as variable as the cells and include solid, alveolar, papillary, tubular and cystic arrangements. Large thin-walled sinuses ready to receive invading cells are a characteristic feature of this tumor. Foci of necrosis, calcification, desmoplasia and old and recent hemorrhage vary the picture. Prognosis on the basis of cell type is not reliable. The size of the tumor is the principal factor in prognosis.

B. Tumors of the Renal Pelvis. These tumors can be divided approximately as follows: papillomas 30%; papillary epidermoid carcinomas 45% non-papillary carcinomas 25%. Mucous adenocarcinomas are rare. There are two features of tumors of the renal pelvis that deserve special emphasis. Papillary cancer may appear deceptively benign; papillary neoplasms of the renal pelvis are commonly associated (from 25% to 50%) with similar tumors in the ureter, bladder and the other kidney. The reason for this is probably a neoplastic diathesis of the mucosa of the urinary tract with multicentric origin of the tumors rather than implantation through direct or lymphatic seeding. These tumors are pathologically similar to papillary cancer of the bladder. Microscopic examination shows the central portion of the tumor made up of a connective tissue axis continuous with the submucosal tissue of the pelvis or ureter and there may be small strands of smooth muscle at the base. The epithelium is transitional in type. There is a distinct association with calculi and infection, particularly with those tumors of the non-papillary type. This tissue metastasized through the renal vein and lymphatics thereby worsening the prognosis. Approximately 50% of the patients with renal papillomas do not survive five years, and the prognosis of the remainder of pelvic tumors is much worse. The over-all prognosis

for tumors of the renal pelvis is therefore far worse than for those of the parenchyma.

C. Wilms' Tumor. This is an embryoma which always arises within the renal substance and as it grows the kidney capsule is expanded and surrounds the neoplasm for a considerable period of time before rupturing. Embryomas vary greatly in size; a few are as small as a fist; many are as large as a grapefruit; some have the proportions of a football. The growth tends to be spherical or oblong. The external surface is smoothly rounded or only slightly lobulated. For the most part the neoplasms are solid, though cystic spaces and areas of degeneration are common. The color is gray to grayish white, but some zones may have a pinkish or yellowish tint. The tissue may be quite firm, or else highly cellular and rather soft. On the whole the vascularity is poor, but the surface vessels can be quite large. The neoplasm tends to be sharply demarcated from the compressed kidney substance by a narrow band of connective tissue, but it is impossible to dissect the neoplasm away at such a septum. The kidney may retain a more or less normal contour, but it is more apt to be squeezed into a distorted shape. Likewise, the kidney pelvis may be narrowed, elongated, or otherwise deformed. Tumor tissue may project into the renal pelvis, but in the great majority of cases it does not do so. The tumor metastasized either by invasion of the renal vein or of the retroperitoneal regional lymphatics.

Histologic Features: Microscopic examination shows tissues of many types. Epithelial cells predominate and vary from sheets of rapidly growing embryomatous elements to more or less well-differentiated epithelial-lined spaces which are often reminiscent of renal tubules. Connective-tissue structures are always found to some extent, and indeed they dominate the picture in some specimens. Smooth muscle and immature or even fully developed striated muscle are commonly observed. Small bits of bone and cartilage may be found. The preservation may be good, but hemorrhage and degenerative changes are common. Careful microscopic examination may shows nests of cells within blood vessels.

Prognosis on Basis of Pathologic Findings: A great deal of time has been spent at the Children's Hospital Department of Pathology, Boston, in an effort to classify their embryomas in subdivisions, with the hope of establishing the prognosis in a given case from the histologic findings of the specimen which has been surgically removed. The studies to date have been fruitless, and they are convinced that nothing is to be gained from subclassifying the embryomas. However, a thorough examination of the specimen gives some important information to the surgeon. Extensive hemorrhage and necrosis, rupture of the capsule, extension of tumor through the capsule, or invasion of renal veins are all findings of almost certain fatal import. The absence of all of these changes does not necessarily mean that the outlook will be excellent, because cells may have broken into the blood stream before or during the operation and no evidence of this propagation can be detected by the pathologist. The size of a tumor is no measure of its capability for setting up metastases. A large growth which completely fills the flank may be followed by a permanent cure, whereas two of their smallest tumors had renal veins blocked with tumor cells at the time of operation.

The Wilms' tumor can then be characterized by: (1) occurrence in the early years of life; (2) a variegated histology; (3) complete encapsulation for an undetermined length of time before its membrane is broken; (4) a very high degree of malignancy; (5) common occurrence of hemorrhage and necrosis; (6) a tendency to reach a large size before metastases occur; (7) dissemination by way of the regional lymphatics or by blood stream invasion.

METASTATIC CHARACTER

The tendency of adenocarcinomas to metastasize is directly related to their size. In a series of 149 cases reported by Bell, 66 of 84 measuring over 5 cm. showed metastases, and only 5 of 65 measuring 5 cm. or less had metastasized. Adenocarcinomas spread predominantly by vessel invasion. They can reach veins either by growing toward the hilum or by piercing the capsule and contacting the veins in the perirenal tissue. Thus do adenocarcinomas spread to the lungs, where they grow luxuriantly and form innumerable

spherical nodules. These adenocarcinomas commonly metastasize to bones. Continuous tumor thrombi from the renal vein to the right auricle do occur. Lymphnode metastases are much less frequent than in a Wilms' tumor. In Wilms' tumor metastases are commonly found within the lungs, liver, brain and regional lymph nodes; this spread is also mainly by veins. The ulcerating epidermoid carcinomas quickly metastasize to regional lymph nodes and distant metastases are almost always present when the tumor is first seen. Papillary carcinomas are slow to metastasize and only infrequently show distant spread. Death usually occurs due to recurrence of the tumor or kidney infection.

Finally, I would like to stress the following points: (1) We are dealing with a statistically small group of malignancies which have to date a terribly high lethal end-result. (2) The main tumor is the renal adenocarcinoma, which in its variety of cellular growth may be difficult to classify. This is a tumor of adult life. The term adenocarcinoma should replace the old word "hypernephroma" since there is no good evidence for the theory that these originate from adrenal rests. (3) Wilms' tumors are practically always found in children and rarely above the age of 15, although a few cases in older patients have been reported. (4) The tumors of the renal pelvis, whether papillary or non-papillary, are all malignant and carry a poorer prognosis than both their bladder counterparts and the solid tumors of the renal parenchyma. These pelvic tumors also are associated in a large percentage of cases with renal infection and renal calculi. (5) The other tumors, about which I have said very little, are clinically insignificant, although pathologically extremely fascinating since they involve the kidney in some relation with maany disease processes in the body. The possible relationships between renal lipomata and fat metabolism, renal hemangiomas with vascular diseases, endometriosis of the kidney and endometriosis elsewhere, hamartomas associated with tuberous sclerosis, adenomas with Lindau's disease (angiomas of the retina and cerebellum), leukemic infiltration associated with tuberous sclerosis, adenomas with Lincomas with primary disease beginning elsewhere, provide endless avenues for speculation and investigation. Renal tumors, like malignant tumors elsewhere in the body, present a considerable challenge primarily in the field of detection. In the light of our present knowledge it is only by early diagnosis that an opportunity to treat and cure is possible. It would be helpful to the urologist if out of studies being made of the pathology of these tumors some increased prognostic significance could be obtained.

THE TREATMENT OF RENAL TUMORS*

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The treatment of renal tumor is nephrectomy, after the diagnosis is made, provided the patient has another kidney capable of sustaining life. The method of nephrectomy depends upon the skill and experience of the surgeon performing it. Each man uses the approach best suited for him, keeping the welfare of the patient in mind. Survival rates are about the same no matter what method of approach is used. Early ligation of the renal pedicle, with as complete removal of the perirenal fat as possible and gentleness in handling the kidney, is required regardless of the approach.

The Nagamatsu or dorsolumbar flap incision, which you will see demonstrated by a motion picture made here in Wilmington, is a relatively new method of approach. It appears to have several advantages over the transthoracic route. The transabdominal approach may be very useful when the tumor is of very large size. The Sweetser incision, which is a conventional kidney incision carried forward through the rectus muscle and then upward along the medial border of the rectus, may be very helpful in obtaining exposure where large tumors are concerned. With this incision the patient is lying on his side and the peritoneum is not opened.

The nine most common kidney incisions are: (1) the usual oblique kidney incision; (2) the transverse flank incision; (3) the vertical transperitoneal incision; (4) Sloan's incision; (5) Young's incision; (6) Cabot's incision;

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(7) Sweetser's incision; (8) the trans-thoracic approach; and (9) the dorsolumbar flap incision.

N. C. Foot, G. A. Humphreys and W. F. Whitmore (Cornell University) studied and classified 295 cases of kidney tumor. "Of 85 patients with renal cell carcinoma treated by nephrectomy 38% were alive 5 years later. 4 with proved metastases before operation did not survive 3 years, and of 40 with renal cell carcinoma 22% were alive 10 years after nephrectomy. A few patients in whom metastasis developed postoperatively survived many months, some receiving palliative x-ray therapy. Survival beyond 5 years does not imply cure, since these tumors grow slowly and often require 10 years of observation for evaluation of prognosis."

C. E. Burford, J. E. Glenn and E. H. Burford (Washington University) followed 110 patients for more than six months. "The treatment of choice in their opinion was nephrectomy with postoperative deep x-rays for hypernephromas and pre- and postoperative deep x-rays for Wilms' tumor which was 7.3% in their series. Nephroureterectomy was used for intrapelvic tumors."

SUMMARY: Nephrectomy is the treatment of choice in renal tumors, followed by x-ray treatment. In Wilms' tumor preoperative as well as postoperative x-ray treatment may be given.

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$9200 For A Medical Diploma

Medical college training in America costs approximately $9,200 today. That's what the average student spends for four years in medical school, according to a report published in the February issue of the Journal of MEDICAL EDUCATION.

The study, by John M. Stalnaker and Sarah Counts of the Association of American Medical Colleges, was based on questionnaires sent to students at 26 medical schools throughout the country. The $9,200 does not cover the cost of premedical training, interneship and residency training, or the cost to the young physician of setting himself up in practice.

One-third of the 6251 students who answered expect to be in debt when they graduate from medical school, to the tune of approximately $3500. Most of the students showed reluctance to borrow money from their parents, but 95 per cent reported that they could obtain money for emergency expense from various sources.

About half (48 per cent) of the students who replied are single and living away from home. Most of the money for medical education for the single student comes from his parents, while the married student is supported largely by the earnings of his wife. Income for the students varies widely, with an average of $2450. Vacation earnings contribute only a small amount, a median of $550.

The fathers of about one half of the medical students participating in the survey are engaged in professional, executive or managerial occupations, with 10 per cent of the group being sons of physicians. Parents' annual income averaged $7000.

The study was undertaken to provide factual data for students interested in medicine, for their parents and their college advisors.

American Medical Association Dues

Reference Committee on Amendments to the Constitution and Bylaws.

"The Committee has considered that portion of the report of the secretary on payment of back dues which is found on Page 33 of the Handbook. This refers to a resolution presented to the House of Delegates in June 1953 by George A. Earl of Minnesota concerning the payment of membership dues. This Committee presents a substitute resolution as follows:

> 'RESOLVED, that any active member of the American Medical Association who failed to pay dues for the year 1950, and who was suspended for such delinquency, may be reinstated during the first six months of 1954 by payment of 1954 dues only.
>
> Should such an individual fail to pay his 1954 dues by July 1, 1954, he shall continue to be considered delinquent.' "

+ Editorials +

DELAWARE STATE MEDICAL JOURNAL

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Footnotes and bibliographies should conform to the style of the Quarterly Cumulative Index Medicus, published by the American Medical Association, Chicago.

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Vol. 26 February, 1954 Vol. 2

The A. M. E. F. Appeals

The annual solicitation for funds for the medical schools by the American Medical Education Foundation is beginning all over the United States. Last year the physicians of the country gave, through the A. M. E. F., one million dollars. This must be doubled in 1954 if the present quality of instruction is to be maintained.

Industry is more and more interested as it sees how the doctors respond. Big business donated to our medical schools $600,000 in 1951; $700,000 in 1952; and last year 1,000 firms gave $1,300,000. When corporations are asked to give, they ask four questions: (1) What is the benefit to our company? (2) Is there a real need? (3) Are we allowed to give? (4) Don't the doctors contribute to their schools? It is their problem. Let 200,000 of them give $50 each and you will have your 10 million.

It is a fact that a lot of our members give directly in addition to what the A. M. E. F. collects, but so does industry. Many a corporation gives directly to local hospitals, to special research funds, and to medical school building programs, but the real need lies in maintaining and improving the present good quality of instruction.

You probably do not know that the U. S. Government gives 32 million dollars annually for special research and specifies that it be spent for specific programs. (See The Journal, January, 1954, page 26.) However, each school has to have extra money to follow-through with this research. It really costs the medical school money and they do not have the money.

If the government takes over the medical schools entirely, (1) all other sources of income to the schools will stop. What the Congress gives will be all that they will get. (2) The amount allotted to each school will vary from year to year, depending upon who is elected to Congress. And, (3) the government will then also say who can go to medical school and who can not, and will say what the graduates shall and shall not do, forever afterwards.

The aim of the A. M. E. F. is to keep the medical schools *free, solvent,* and *progressive.*

Papers Wanted

The program for the next meeting of the Medical Society of Delaware, Dover, October 11-13, 1954, is now being prepared. Members who wish to present papers at this meeting should contact the Executive Secretary promptly, giving the title and a fifty word abstract of the proposed paper.

THE MONTH IN WASHINGTON

Washington, D. C., Feb. 9—Some parts of the Eisenhower administration's broad health program are making good progress on Capitol Hill, while others are virtually standing still or bogged down in the technical complications that are always a threat to new legislation. Well ahead of the other proposals, and possibly destined for enactment, are bills to broaden the scope of the Hill-Burton hospital construction law and to liberalize income tax deductions for medical expenses.

The House Interstate and Foreign Commerce Committee, under chairmanship of Rep. Charles Wolverton (R., N.J.), wound up its long fact-finding study of voluntary health insurance plans and immediately started hearings on the Hill-Burton changes. The purpose is to amend the Hill-Burton law so that it can be used to disburse federal grants to states for construction of health facilities that do not qualify as "hospitals." The administration is anxious to stimulate the building of more nursing homes, hospitals for the chronically ill, diagnostic or treatment center, and rehabilitation facilities.

An initial appropriation of $2 million would be authorized for surveys and planning, and $60 million annually for three years of construction. Per capita income as well as population would be used to determine a state's share, as under the present Hill-Burton program.

At the House hearing, crowded into two days, the construction program was indorsed at least in principle by every witness, except the representative of the American Association of Nursing Homes. Because the program is limited to non-profit sponsors, members of this group could not receive grants. Their spokesman said long-term loans through the Small Business Administration would help solve their problem.

American Medical Association recommended passage of the bill, but urged that facilities for the chronically ill and the handicapped be "part of or near a conventional hospital," and that facilities of all types be open to the entire community without discrimination, as in the present Hill-Burton law. (It is likely hearings also will be held on this legislation in the Senate.)

The House Ways and Means Committee, meanwhile, was giving its approval to a new income tax provision that would allow the deduction of medical expenses if they exceed 3% of adjusted gross income, rather than 5% under present law. The present maximum limitation would be doubled, and the deduction of travel expenses allowed where travel is prescribed by a physician. These changes—a long-time AMA goal—are embodied in the omnibus tax readjustment bill.

President Eisenhower's proposal for federal reinsurance of voluntary health plans has not been able to follow the steady course on which it first appeared to be embarked. At the House hearings, none of the spokesmen for the large organizations in the health fields—AMA, Blue Cross and Shield, American Hospital Association—was willing to indorse the plan. Like the AMA spokesmen, most of them wanted first to examine the actual administration bill, which at that time had not been introduced. From the Blue Cross, however, came a suggestion that the idea be tried out experimentally.

Spokesmen for national labor organizations expressed mixed reactions, with some maintaining that reinsurance was a poor substitute for what they believe the country really needs—national compulsory health insurance.

The administration's health budget for the next fiscal year, starting next July 1, calls for a slight overall reduction. The regular Hill-Burton program, currenty operating on $65 million, would get $50 million (any appropriation to start the proposed expanded construction would be in addition). Relatively sharp reductions would be made in funds for venereal, tuberculosis and communicable disease control, in line with policy of shifting this responsibility to the states. The various research institutes would receive about what they are now spending.

One of the few new items is for $7.8 million, estimated as necessary for the extra cost of enlarging the federal program of vocational rehabilitation. Legislation authorizing the expansion is awaiting Congressional action. The administration hopes gradually to increase the number of persons rehabilitated annually from the current 60,000 to 200,000. While the program is being stepped up, one of its goals

would be to induce states to increase their spending until eventually their appropriations match the federal. Like most of the President's health program, the rehabilitation effort has the support of the AMA.

Conferences between AMA officials and administration leaders are continuing. Latest sessions were with Secretary Hobby, concerning her department's legislative plans; with VA Administrator H. V. Higley, on treatment of non-service connected cases; and with Adm. Arthur W. Radford, chairman of the Joint Chiefs of Staff, Dr. Frank Berry, Assistant Defense Secretary for health and medical matters, and Dr. Howard A. Rusk, chairman of the Health Resources Advisory Committee, on medical care for military dependents. Representing the AMA at one or more of the meetings were Drs. Walter B. Martin, David B. Allman, Gunnar Gundersen, Louis Orr, James C. Sargent, W. L. Crawford, George F. Lull, Ernest B. Howard and Frank E. Wilson.

Earlier, AMA representatives talked over legislation with President Eisenhower at the White House.

OBITUARY

WILBUR E. POSTLES, M. D.

Dr. Wilbur E. Postles, a practicing physician in Wilmington for over 49 years, died on February 5, 1954, shortly after being stricken at his home, with a cerebral hemorrhage, aged 79. The veteran physician had planned to retire next December on completion of a half century in the medical profession. His office always had been located at his home on Market Street.

Born near Frederica, Dr. Postles was graduated from Wesley College, Dover, and the Hahnemann Medical College, Philadelphia, in 1904. He set up his practice in Wilmington and had remained here. He was regarded as "an institution" in the upper Market Street neighborhood.

Dr. Postles was a member of the Memorial Hospital staff, the New Castle County Medical Society, the Medical Society of Delaware, and the American Medical Association. He also was active in Masonic lodges and had been presented with a life membership in Oriental Lodge, A. F. and A. M. He also belonged to St. John's Chapter, No. 4, RAM; St. John's Commandery, and Lu Lu Temple of the Shrine. He was an extensive traveler.

Surviving are his wife, Mrs. Mildred B. Postles; a daughter, Mrs. Audrey W. Allen, Pomona, Calif.; a niece, Mrs. George R. Miller, Jr., wife of the superintendent of the State Department of Public Schools, and three grandchildren.

The funeral was held on February 9, 1954, with interment at Barratt's Chapel, near Frederica.

BOOK REVIEWS

Respiratory Diseases and Allergy. By Josef S. Smal, M. D. Pp. 80. Cloth. Price, $2.75. New York: Medical Library Company, 1953.

The author describes his method of treating respiratory diseases and allergy as a new approach. He states that all of the upper respiratory diseases are due to allergy only and not due to acute contagious attacks caused by newly-implanted virulent organisms. He refers to these diseases as "respirallergy." The new treatment consist of giving the patient three stock vaccines separately, that is, (1) ragweed; (2) dust; (3) catarrhal vaccine. The routine schedule of dosage is outlined. The limitation of the common food offenders (milk, cream, cheese, and sugar) is part of the treatment. Cortone is prescribed for severe cases, and other symptomatic drugs are employed.

Infectious diseases of the respiratory tract are described briefly in a general way and should be checked with present-day literature for detailed treatment.

This little book is well written although it has considerable repetition. It contains no scientific evidence and, as the author admits, his results are based on his own practical experience.

The book is worth having if for no other reason than the emphatic and convincing way in which the author succeeds in making the physician allergy-minded in all respiratory diseases.

The Nursing Mother. By Frank Howard Richardson, M. D. Pp. 204. Cloth. Price, $2.95. New York: Prentice Hall, Inc., 1953.

It seems that interest in "returning back to nature" is being revived in breast feed-

ing. This is not only justified by the superior results noted in the growth and nutrition of nursing babies, but it is also important from the standpoint of the deeper affection which results from the closer association of mother and child.

No one can deny that cows produce a nutritious milk but it must also be admitted that the human elements, such as antibodies, minerals, enzymes, hormones, and other factors known and unknown, are unquestionably superior in the human milk.

The last chapter consists of questions frequently asked by expectant mothers. The answers are clear and concise. An index adds to the practical value of this book as a reference. It is a very informative and excellently written book for the medical profession and for parents.

Living With a Disability. By Howard A. Rusk, M. D., and Eugene J. Taylor, in collaboration with Muriel Zimmerman, O. T. R. and Julia Judson, M. S. Pp. 207. Cloth. Price, $3.50. Garden City, New York: The Blakiston Company, 1953.

Dr. Rusk and his associates have revolutionized the care of the handicapped. The disabled person is taught to realize that he can become independent with training and mechanical aids.

This book is richly illustrated with photographs of numerous practical devices which will help persons with all degrees of disability.

Working situations for the disabled person are illustrated so that life can really be made useful at home, in the office, and in the shop.

All physicians, disabled persons, and those who are interested in rehabilitation should have a copy of this book.

Fool's Haven. By C. C. Cawley. Pp. 210. Cloth. Price $2.75. Boston. House of Edenboro, 1953.

This interesting novel attempts to emphasize the problem of faith healing and its damaging effect in indirectly causing the death of a child because of neglect on the part of the parent or guardian in failing to call for medical aid.

The plot revolves about a mother who bases her reliance on prayer instead of doctors, because doctors had failed to save her husband's life and that a neighbor's son died after an operation for appendicitis. The facts that her husband's disease was incurable and that the neighbor's son had not been given medical attention until too late are not considered as important.

The pastor of her church, a self-ordained minister with a questionable reputation, obtains her confidence and she places herself and her family in his hands and those of the church elders. Her daughter dies of a ruptured appendix which resulted after several attacks were "healed" by prayer. The mother was tried and convicted of manslaughter but her pastor, who had convinced the mother to keep the girl away from medical attention, was found not guilty as the law did not regard him as having any legal obligation to provide medical care for the girl. However, he emphatically stated to a relative of the mother that "Mrs. Dunn and her daughter Carol have turned to the Greatest Physician of all. You can have God or you can have a doctor, but when you go to a doctor, it only shows that you do not, after all, have complete faith in God and in prayer. You cannot have both God and a doctor."

The author brings out a very important issue for which only the church and the medical profession can recommend legislation to enlighten these misinformed people who confuse religion with scientific improvements in our daily living. Certainly the many denominational hospitals operated by the several well-recognized churches are not in error when they combine prayer and all scientific knowledge to help suffering humanity.

It is true that death will come sooner or later, and it is also true that medical science does not save every sick person but that is no reason why we should revert to the dark ages when life expectancy was only a few years in comparison to the 69 years of today. We would like to agree with religion, that it has been because of the prayer and the divine powers given to scientists that all of the many comforts and improvements in our daily living have been made.

The author of this book and the publishing company should be congratulated for their foresight and courage in bringing this subject of faith healing to the attention of the people.

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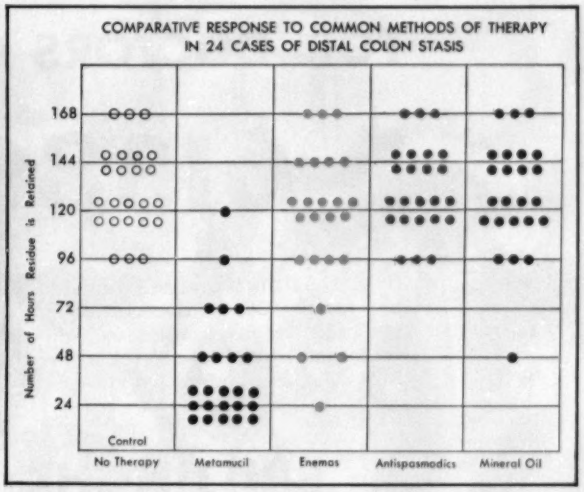
Distal Colon Stasis



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*Barowsky, H.: A Roentgenographic Evaluation of the Common Measures Employed in the Treatment of Colonic Stasis. Rev. Gastroenterol. *19*:154 (Feb.) 1952.

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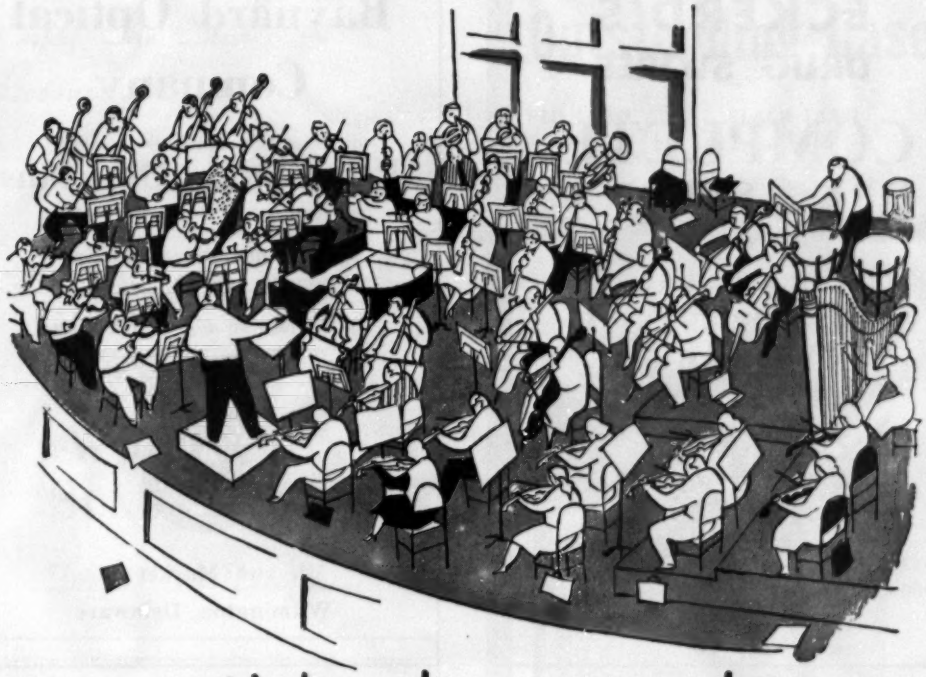

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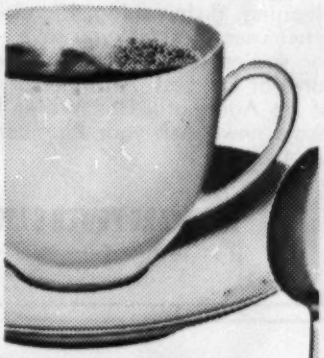

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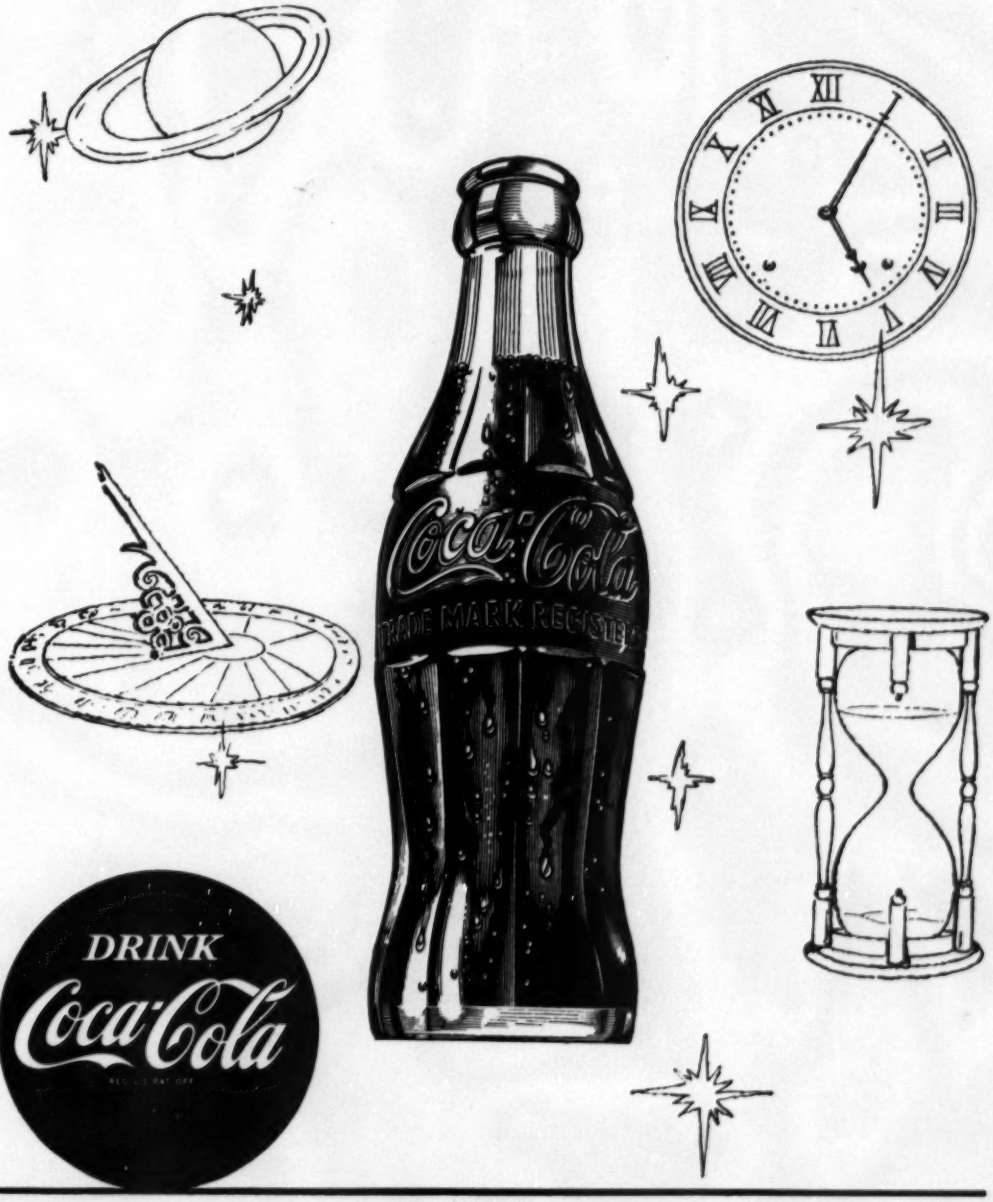

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